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# [1,2]- or [2,3]-Rearrangement of Onium Ylides of Allyl and Benzyl Ethers and Sulfides via in Situ-Generated Iodonium Ylides

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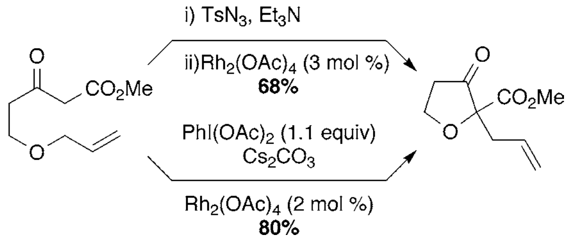
## ABSTRACT



**Iodonium ylides, generated in situ with bisacetoxyiodobenzene, are converted to allyl- or benzyl-substituted oxonium or sulfonium ylides via rhodium- or copper-catalyzed carbene transfer. Except for the *S*-benzyl example, the resulting ylides undergo rearrangement to the corresponding 2-substituted heterocycles. This demonstrates the first use of iodonium ylides as diazoketone surrogates for the generation and rearrangement of onium ylide intermediates. This abbreviated one-step method proceeds in comparable yields relative to the corresponding two-step route employing diazoketone intermediates.**

Diazoketones give rise to a wide variety of chemistry, typically via their derived metallocarbenes, including C−H insertion, cyclopropanation, and ylide formation.[1] However, widespread adoption of methods employing these intermediates has been limited, perhaps in part because of their potentially hazardous properties. Recently, iodonium ylides have received a great deal of attention as surrogates for diazocarbonyl compounds in metallocarbene-mediated processes.[2] This approach has been very successful in the areas of C−H insertion,[3] cyclopropanation,[4] and dipolar cycloadditions.[5]

Previous studies from our group have established the synthetic value of rearrangement processes involving cyclic oxonium ylides.[6] In particular, Stevens [1,2]-shifts of acetal-derived oxonium ylides offer a convenient entry to medium-sized carbocycles and cyclic ethers.[7] However, these methods require the prior formation of diazoketone substrates, whose preparation is not uniformly efficient. Here, we describe the first application of in situ-generated iodonium ylides for the formation and rearrangement of oxonium and sulfonium ylides. This process entails an overall one-step conversion of simple $\beta$-ketoesters with pendant allyl or benzyl ethers or sulfides to cyclic ethers or sulfides.

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[1] Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1997.

[2] (a) Müller, P. *Acc. Chem. Res.* **2004**, *37*, 243−251. (b) Kirmse, W. *Eur. J. Org. Chem.* **2005**, 237−260.

[3] Camacho, M. B.; Clark, A. E.; Liebrecht, T. A.; DeLuca, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 5210−5211.

[4] (a) Dauban, P.; Saniere, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707−7708. (b) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327−2329. (c) Müller, P.; Ghanem, A. *Org. Lett.* **2004**, *6*, 4347−4350.

[5] Müller, P.; Chappellet, S. *Helv. Chim. Acta* **2005**, *88*, 1010−1021.

[6] (a) Marmsäter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144−5145. (b) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027−2040. (c) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Org. Lett.* **2004**, *6*, 1657−1660.

[7] (a) Tester, R. W.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 4631−4634. (b) Marmsäter, F. P.; Murphy, G. K.; West, F. G. *J. Am. Chem. Soc.* **2003**, *125*, 14724−14725. (c) Murphy, G. K.; West, F. G. *Org. Lett.* **2005**, *7*, 1801−1804. (d) Murphy, G. K.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2006**, *84*, in press.

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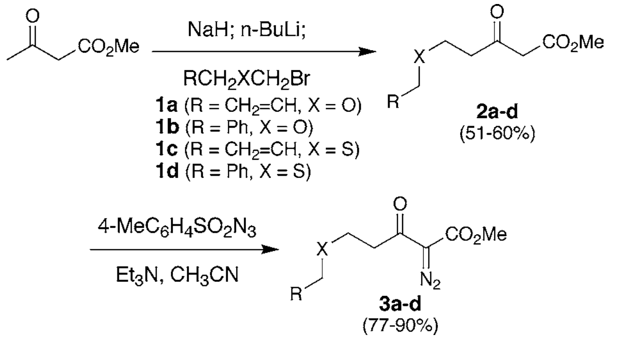
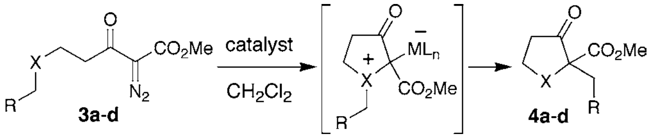
To explore the feasibility of this approach, we prepared several substrates via the monoalkylation of the dianion of methyl acetoacetate[8] with bromomethyl ethers and sulfides **1a**−**d**[9] to give **2a**−**d** in moderate yield (Scheme 1). Diazo-transfer[10] using *p*-toluenesulfonyl azide then afforded diazoketoesters **3a**−**d**.

**Scheme 1**



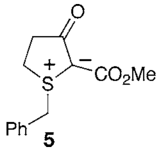
Initial experiments were carried out using the diazo substrates **3a**−**d** and either copper(II) bis(hexafluoroacetylacetonate) ($Cu(hfacac)_2$) or $Rh_2(OAc)_4$ (Table 1). These catalysts were chosen for their broad applicability in various onium ylide-mediated processes.[11] In the event, substrates **3a**−**c** underwent conversion to the corresponding tetrahydrofuranones **4a**,**b** or tetrahydrothiophenone **4c** with either catalyst. Product **4b**, resulting from a benzyl [1,2]-shift, was formed in only moderate yields (entries 3 and 4). This result is consistent with previous observations regarding the relative efficiency of [1,2]- and [2,3]-shifts of oxonium ylides.[6] Sulfide **3c** required longer reaction times (entries 5 and 6), possibly because of a combination of catalyst deactivation by sulfur[12] and the decreased reactivity of sulfonium ylides as compared to their oxonium counterparts. Finally, the *S*-benzyl substrate **3d** furnished only the intermediate sulfonium ylide **5** under the reaction conditions. Isolation of the ylide intermediate may occur because of the relatively high barrier for a Stevens [1,2]-shift (presumed to involve initial homolytic cleavage) together with the aforementioned lower reactivity of sulfonium ylides.[13] Moody has observed a similar result with the homologous ylide **6**.[14]

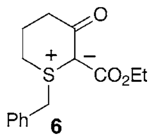
**Table 1.** Carbene-Transfer and Ylide Rearrangement Reactions of Diazocarbonyl Substrates **3a**−**d**[a]



| entry | substrate | R | X | catalyst | time (h) | product (% yield)[b] |
|---|---|---|---|---|---|---|
| 1 | **3a** | $CH_2{=}CH$ | O | $Rh_2(OAc)_4$ | 0.2 | **4a** (88) |
| 2 | **3a** | $CH_2{=}CH$ | O | $Cu(hfacac)_2$ | 1 | **4a** (99) |
| 3 | **3b** | Ph | O | $Rh_2(OAc)_4$ | 1 | **4b** (39) |
| 4 | **3b** | Ph | O | $Cu(hfacac)_2$ | 16 | **4b** (34) |
| 5 | **3c** | $CH_2{=}CH$ | S | $Rh_2(OAc)_4$ | 24 | **4c** (63) |
| 6 | **3c** | $CH_2{=}CH$ | S | $Cu(hfacac)_2$ | 24 | **4c** (89) |
| 7 | **3d** | Ph | S | $Rh_2(OAc)_4$ | 24 | **5**[c] |
| 8 | **3d** | Ph | S | $Cu(hfacac)_2$ | 24 | **5**[c] |

[a] Substrates in $CH_2Cl_2$ were added dropwise by cannula to a mixture of catalyst (3 mol % of $Rh_2(OAc)_4$ or 10 mol % of $Cu(hfacac)_2$) in $CH_2Cl_2$ and stirred until complete consumption was observed. Reactions employing $Rh_2(OAc)_4$ were carried out at room temperature, whereas those using $Cu(hfacac)_2$ were carried out at reflux. [b] Yields are for isolated material after chromatography. [c] Sulfur ylide **5** was the only product observed in the crude reaction mixture. Yields are not reported because only small amounts of pure material were isolated for analytical purposes (see Supporting Information).


**5**


**6**

Using the results above as a baseline, we next set out to examine possible conditions for direct generation of the ylide intermediates from ketoesters **2a**−**d** via in situ formation of iodonium ylides (Table 2). Initial experiments using substrate **2a** employed conditions previously shown to be effective in other types of carbene-transfer processes mediated by in situ-generated iodonium ylides.[4c,15] We were gratified to find that treatment of **2a** in MeOH with a slight excess of $PhI(OAc)_2$, 2 equiv of KOH, and catalytic $Rh_2(OAc)_4$ (entry 1) did indeed furnish oxonium ylide rearrangement product **4a** in reasonable yield (55%), albeit clearly inferior to the overall yield of the two-step sequence employing the initial diazo-transfer reaction (see Scheme 1 and Table 1, entry 1). Incremental improvements were seen when the solvent was changed to $CH_2Cl_2$ and $K_2CO_3$ was substituted for KOH (entries 2 and 3). Optimal results were obtained with the base $Cs_2CO_3$, furnishing the product **4a** in 80% yield (entry 4).[16] These conditions were then applied to the other three substrates. Both **2b** (entry 6) and **2c** (entry 8) were converted to the desired cyclic products in yields well above those obtained by the two-step procedure. On the other hand, $Cu(hfacac)_2$ was found to be substantially inferior under the in

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(8) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082−1087.

(9) (a) Kawasaki, T.; Kimachi, T. *Tetrahedron* **1999**, *55*, 6847−6862. (b) Reich, H. J.; Jasperse, C. P.; Renga, J. M. *J. Org. Chem.* **1986**, *51*, 2981−2988.

(10) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733−749.

(11) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892−6894.

(12) (a) Davies, H. M. L. In *Nitrogen, Oxygen and Sulfur Ylides in Synthesis: A Practical Approach*; Clark, J. S., Ed.; Oxford University Press: Oxford, 2002; pp 156−163. (b) See also: Felthouse, T. R. *Prog. Inorg. Chem.* **1982**, *29*, 73−154.

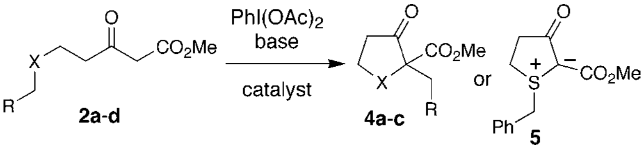
(13) Extended heating of sulfonium ylide **5** in toluene failed to effect the desired [1,2]-shift process.

(14) Moody, C. J.; Taylor, R. J. *Tetrahedron* **1990**, *46*, 6501−6524.

(15) Prakash, O.; Sharma, V.; Tanwar, M. P. *Can. J. Chem.* **1999**, *77*, 1191−1195.

(16) Treatment of **2a** with $PhI(OAc)_2$ and base in the *absence* of any catalyst and in new glassware furnished low yields of **4a** in the same time frame as the $Rh_2(OAc)_4$-catalyzed reaction, indicating the existence of a minor background uncatalyzed process.

**Table 2.** Carbene-Transfer and Ylide Rearrangement Reactions of $\beta$-Ketoester Substrates **2a**−**d**[a]



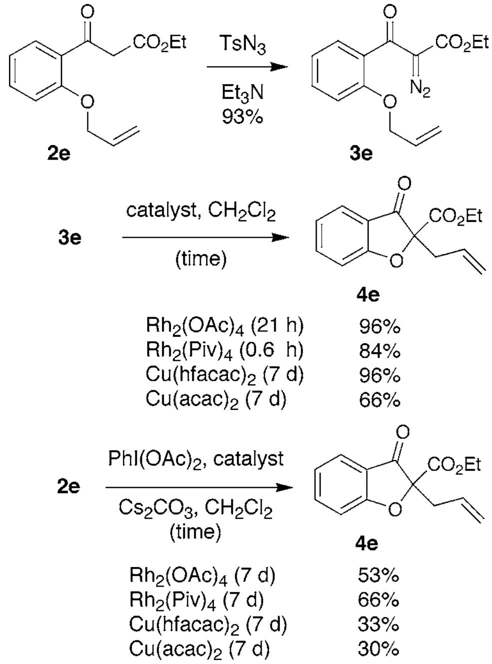
| entry | substrate | base | catalyst | time (h) | product (% yield)[b] | two-step yield[b,c] |
|---|---|---|---|---|---|---|
| 1 | **2a** | KOH[d] | $Rh_2(OAc)_4$ | 1.5 | **4a** (55) | 68 |
| 2 | **2a** | KOH | $Rh_2(OAc)_4$ | 8 | **4a** (63) | 68 |
| 3 | **2a** | $K_2CO_3$ | $Rh_2(OAc)_4$ | 3 | **4a** (67) | 68 |
| 4 | **2a** | $Cs_2CO_3$ | $Rh_2(OAc)_4$ | 12 | **4a** (80) | 68 |
| 5 | **2a** | $Cs_2CO_3$ | $Cu(hfacac)_2$ | 10 | **4a** (9) | 77 |
| 6 | **2b** | $Cs_2CO_3$ | $Rh_2(OAc)_4$ | 0.5 | **4b** (41) | 35 |
| 7 | **2b** | $Cs_2CO_3$ | $Cu(hfacac)_2$ | 12 | [e] | 31 |
| 8 | **2c** | $Cs_2CO_3$ | $Rh_2(OAc)_4$ | 19 | **4c** (78) | 55 |
| 9 | **2c** | $Cs_2CO_3$ | $Cu(hfacac)_2$ | 64 | **4c** (32) | 77 |
| 10 | **2d** | $Cs_2CO_3$ | $Rh_2(OAc)_4$ | 24 | **5**[f] | |
| 11 | **2d** | $Cs_2CO_3$ | $Cu(hfacac)_2$ | 14 | **5**[f] | |

[a] All reactions (except entry 1) were carried out in 0.05 M $CH_2Cl_2$ at room temperature using 1.1 equiv of $PhI(OAc)_2$, 2.1 equiv of base, and 3 mol % of $Rh_2(OAc)_4$ or 10 mol % of $Cu(hfacac)_2$. Reactions were worked up when judged complete by TLC or GC analysis. [b] Yields are for isolated material after chromatography. [c] Overall yield for the alternative two-step diazotransfer/carbene-transfer process per Scheme 1 and Table 1. [d] The experiment described in entry 1 was carried out in MeOH. [e] Product **4b** was not detected in the reaction mixture despite extended reaction times. [f] Sulfur ylide **5** was the only product observed in the crude reaction mixture. Yields were not determined in these cases.

situ activation conditions (entries 5, 7, and 9). Reductive activation of copper(II) catalysts by a sacrificial quantity of diazocarbonyl compounds has been suggested to occur prior to various copper-catalyzed carbene-transfer processes;[17,18] the absence of any diazoketone in these experiments may be responsible for the low conversion seen in these cases. Finally, as in the diazo substrates, the *S*-benzyl case gave only the unreactive sulfur ylide **5**.

Next, aromatic ketoester **2e** was prepared and subjected to diazotransfer to give the known substrate **3e**[19] (Scheme 2). Diazo compound **3e** underwent efficient conversion to dihydrobenzofuranone **4e** using a variety of rhodium(II) or copper(II) catalysts. The simple ketoester **2e** could also be converted to **4e**, but yields were moderate and required extended reaction times. Thus, in contrast to the simple aliphatic cases from Table 2, the two-step protocol via the diazo compound appears to be superior in this case.

**Scheme 2**



This work describes the first examples of the direct conversion of active methylene-containing compounds to oxonium or sulfonium ylides via in situ-generated iodonium ylide and metallocarbene intermediates. Rearrangement products (via a [1,2]- or [2,3]-shift) are formed efficiently and, for the simple acyclic substrates **2a**−**c**, in yields comparable to the corresponding two-step protocol employing diazocarbonyl intermediates. Substrate **2d**, containing an *S*-benzyl substituent, underwent conversion to the sulfonium ylide without subsequent rearrangement, and this product was fully characterized. Further applications of this methodology are presently under study and will be reported in due course.

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**Supporting Information Available:** Experimental procedures and spectral data for all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300−3310. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−936. (c) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977−1050.

(18) For other discussions regarding reductive activation of copper(II) catalysts, see: (a) Wulfman, D. S. *Tetrahedron* **1976**, *32*, 1231−1240. (b) Dauben, W. G.; Hendricks, R. T.; Luzzio, M. J.; Ng, H. P. *Tetrahedron Lett.* **1990**, *31*, 6969−6972. (c) Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* **1997**, *53*, 9599−9610. (d) Kirmse, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1088−1093.

(19) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060−6062.